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(54) Title: PROCESS FOR THE PREPARATION OF AMORPHOUS ATORVASTATIN CALCIUM

(57) Abstract: The present invention relates to a process for the preparation of amorphous atorvastatin calcium. In essence, the process comprises dissolving form - I or a mixture of crystalline and amorphous atorvastatin calcium in a solvent consisting of an aliphatic acyclic ketone, filtering the solution and removing the solvent at 40 to 50 °C under vacuum.

PROCESS FOR THE PREPARATION OF AMORPHOUS ATORVASTATIN CALCIUM

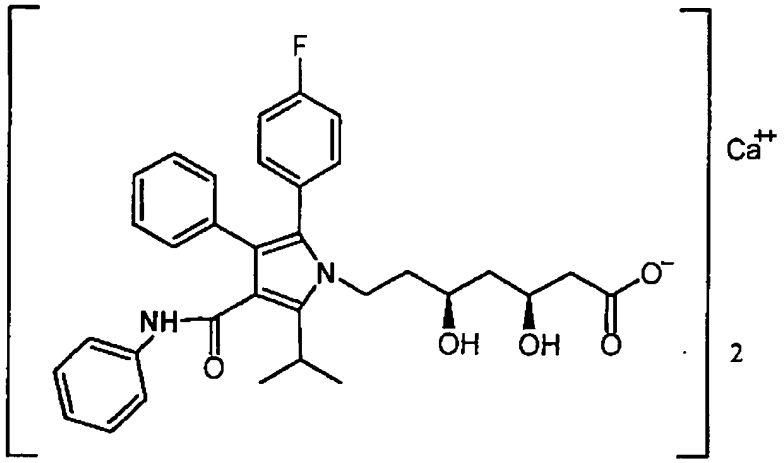
Field of invention

The present invention relates to a process for the production of amorphous atorvastatin calcium.

Background of the invention

Atorvastatin, the substance known by the chemical name [R-(R*,R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL) PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID is a member of the class of drugs called statins. Statin drugs are currently the most therapeutically effective drugs available for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. Open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized.

According to the disclosure contained in the U.S.Patent No. 5273995, R-form of the ring opened acid form has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula 1 is more suited for formulations and has been recommended as a drug.



United states patents 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,273,995; 5,280,126; 5,298,627; 5,342,952; 5,385,929; 5,397,792; European Patent 409,281; and PCT publication No. 8,907,598 describe various processes and key intermediates for preparing atorvastatin.

Atorvastatin is preferably prepared as its calcium salt, i.e. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2 : 1) since the calcium salt is desirable and it enables easy formulation of atorvastatin for example, tablets, capsules, lozenges, powder and the like for oral administration. Different polymorphic forms of atorvastatin calcium such as Form I, Form II, Form III, Form IV, Form V and amorphous form have been reported in WO 97/03958, WO 97/03959, WO 97/03960 and WO 01/36384.

It is known that the amorphous forms in a number of pharmaceutical substances exhibit different dissolution characteristics and bioavailability patterns compared to crystalline forms (Knno T. Chem. Pharm. Bull. 1990, 38, 2003-2007). In some therapeutical indications the bioavailability is one of the key parameters determining the form of the susbstance to be used in a pharmaceutical formulation. Since process for the crystallization and the preparation, respectively of the amorphous substance are sometimes difficult to be performed and as a result the product obtained is in a mixture of amorphous and crystalline form. There is a constant need for processes which enable the preparation of atorvastatin in an amorphous form without simultaneous formation of crystalline forms or which will enable the conversion of crystalline forms into the amorphous form.

Atorvastatin calcium is very slightly soluble in water and it has been found that the crystalline form is less readily soluble than the amorphous form, which may cause problems in the bioavailability of atorvastatin. It has been found that the production of amorphous atorvastatin accordingly to the previously disclosed processes was not consistently reproducible. Therefore various processes have been developed for converting the crystalline form in to amorphous form.

WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin calcium to the amorphous form. Process disclosed therein comprises dissolving crystalline form I atorvastatin in a non-hydroxylitic solvent like tetrahydrofuran or mixture of tetrahydrofuran and toluene. The process involves complete removal of the solvent under high temperature (about 90°c) and under high vacuum (about 5 mm) for 3-5 days. Exposure of the material to high temperature for several days may lead to degradation of the product. This makes the process very inconvenient to operate on a large scale. Slow removal of solvent at a manufacturing scale renders this process as less productive.

The process for the preparation of amorphous atorvastatin described in WO 00/71116 involves dissolving crystalline form in tetrahydrofuran and reprecipitating amorphous atorvastatin by adding cyclohexane or n-hexane n-heptane.

WO 01/28999 describes the purification of crude amorphous atorvastatin calcium by dissolving crude amorphous material in large excess of boiling ethanol or 2-propanol and filtering the hot solution and recovering the material at low temperature.

WO 01/42209 describes the preparation of amorphous atorvastatin calcium from form I by dissolving crystalline form in about 20 – 25 times of methanol, ethanol or acetone, concentrating the solution by distillation and precipitating the product by adding diethylether. The process disclosed therein also is not recommended for commercial production of amorphous atorvastatin calcium due to the use of large excess of diethylether, which may not be safe on plant level.

Summary of the invention

It is the object of the invention to eliminate the drawbacks of the known procedures and to provide a simple reproducible and economically feasible process for the preparation of high purity and uniformly amorphous atorvastatin calcium.

The procedures to manufacture amorphous atorvastatin calcium disclosed in prior arts employ a large excess of solvent or a mixture of solvents, and removing the solvents at high temperature for a longer period of time. Laboratory trials conducted based on all prior arts give amorphous atorvastatin calcium accompanied with higher level of residual solvents i.e. 10,000 to 20,000 ppm, the level of residual solvents is not reduced even at higher temperature under vacuum. The prolonged heating to reduce the level of residual solvents did not result in decrease of the level of residual solvents, instead an appreciable degradation of the product was observed.

The above object is achieved by process of the invention, which employs a single solvent of aliphatic acyclic ketone group, and the level of residual solvent in final product is less than 5000 ppm which is easily achieved by drying the product at relatively less temperature i.e. 45 to 50 ^{0}C under vacuum for 10 to 15 hours. The amorphous atorvastatin calcium prepared by the process disclosed herein does not show any degradation of the product.

According to the present invention, amorphous atorvastatin calcium is produced by dissolving form - I or a mixture of crystalline and amorphous atorvastatin calcium in aliphatic acyclic ketones filtering the solution and removing the solvent at 45 to 50 ^{0}C under vacuum till desired level of residual solvent below 5000 ppm is achieved providing pure amorphous atorvastatin calcium as revealed by X-ray powder difractogram.

Preferably, the solvent is selected from acetone, 2-butanone, 3-pentanone, 2-pentanone or 2-hexanone. Acetone is the most preferred solvent due to its lowest boiling

point i.e. 56 ^{0}C as compared to other aliphatic acyclic ketones. Employing acetone as a solvent gives desired level of residual solvent in final product at relatively low temperature i.e. 45 to 50^{0}C under vacuum for 10 to 15 hours, while other aliphatic acyclic ketones gives higher level of residual solvents even at higher temperature under vacuum for prolonged heating.

Atorvastatin calcium form - I can easily be dissolved in 10 - 15 volumes of acetone at 45 - 50 ^{0}C while a mixture of crystalline and amorphous atorvastatin calcium requires 30 - 50 volumes of acetone depending on the composition of crystalline and amorphous atorvastatin calcium in a particular mixture.

The invention disclosed herein gives pure amorphous atorvastatin calcium by using atorvastatin calcium form - I or any mixture of crystalline and amorphous atorvastatin calcium demonstrating the wide scope and capability of the process disclosed herein.

Detailed description of the invention

According to the process of present invention form - I of atorvastatin calcium is dissolved in 15 volumes of acetone at 40 - 45 ^{0}C and the solution is filtered to remove suspended and extraneous material. The filtered solution is concentrated at 45 - 50 ^{0}C under vacuum leaving behind approximately 2.5 - 3 volumes of acetone. The concentrated solution of atorvastatin calcium in acetone is placed on glass tray, which is put in vacuum dryer. The remaining acetone is removed at 45 - 50 ^{0}C under vacuum for 2 - 3 hours resulting in the white flakes of amorphous atorvastatin calcium which is uniformly powdered. The powdered amorphous atorvastatin calcium is dried at 45 - 50 ^{0}C under vacuum for 15 hours to get acetone content in final product less than 5000 ppm. X-ray powder difractogram reveals the material to be completely amorphous (figure - 2)

According to the present invention a mixture of crystalline and amorphous atorvastatin calcium is dissolved at 50 - 55 ^{0}C in 30 - 50 volumes of acetone depending on the composition of crystalline and amorphous atorvastatin calcium in the mixture. The solution is filtered to remove suspended particles and extraneous material. The filtered solution is concentrated at 45 - 50 ^{0}C under vacuum leaving behind approximately 2.5 - 3 volumes of acetone. The concentrated solution of atorvastatin calcium in acetone is placed on glass tray, which is put in vacuum dryer. The remaining acetone is removed at 45 - 50 ^{0}C under vacuum for 2 - 3 hours resulting in the white flakes of amorphous atorvastatin calcium, which is uniformly powdered. The powdered amorphous atorvastatin calcium is dried at 45 - 50 ^{0}C under vacuum for 15 hours to get acetone content in final product less

than 5000 ppm. X-ray powder difractogram reveals the material to be completely amorphous (figure - 4)

The present invention will now be described with reference to the following non-limiting Examples and the accompanying drawings in which:

Figure 1 depicts X-ray Powder difractogram of atorvastatin calcium form - I. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Figures 2 depicts X-ray powder difractogram of amorphous atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Figures 3 depicts X-ray powder difractogram of mixture of crystalline and amorphous atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Figures 4 depicts X-ray powder difractogram of amorphous atorvastatin calcium. The horizontal axis presents 2θ and the vertical axis corresponds to peak intensity.

Example : 1

10 g of Atorvastatin calcium form - I was dissolved in 150 ml of acetone at 40 to 45 ^{0}C. The solution was filtered and acetone was removed by vacuum distillation at 45 to 50 ^{0}C leaving behind approximately 30 ml of acetone. The concentrated solution of atorvastatin calcium in acetone was further dried in vacuum oven at 45 to 50 ^{0}C for 3 hours providing white flakes of amorphous atorvastatin calcium which was uniformly powdered. The powdered amorphous atorvastatin calcium was dried at 45 - 50 ^{0}C under vacuum for 15 hours to give 8.5 g white solid material with acetone content in final product being less than 5000 ppm. X-ray powder difractogram revealed the material to be completely amorphous (figure - 2).

Example 2 :

10 g of a mixture of crystalline and amorphous Atorvastatin calcium was dissolved in 500 ml of acetone at 50 to 55 ^{0}C. The solution was filtered and acetone was removed by vacuum distillation at 45 to 50 ^{0}C leaving behind approximately 30 ml of acetone. The concentrated solution of atorvastatin calcium in acetone was further dried in vacuum oven at 45 to 50 ^{0}C for 3 hours providing white flakes of amorphous atorvastatin calcium which was uniformly powdered. The powdered amorphous atorvastatin calcium was dried at 45 - 50 ^{0}C under vacuum for 15 hours to give 8.5 g white solid material with acetone content in final product less than 5000 ppm. X-ray powder difractogram reveals the material to be completely amorphous (figure - 4).

CLAIMS

1. A process for the preparation of amorphous atorvastatin calcium which comprises dissolving form - I or a mixture of crystalline and amorphous atorvastatin calcium in a solvent consisting of an aliphatic acyclic ketone, filtering the solution and removing the solvent at 40 to 50 ^{0}C under vacuum .
2. A process as claimed in claim 1 wherein after dissolving said form - I or a mixture of crystalline and amorphous atorvastatin calcium in -said solvent, the resultant solution is filtered to remove suspended and extraneous material, subjecting resultant solution to partial concentration to leave behind behind approximately 2.5 - 3 volumes of solvent, further removing said solvent in vacuum dryer, grinding white flakes so produced to uniform powder and further drying said uniform powder in vacuum dryer to obtain atorvastatin calcium in amorphous form.
3. A process as claimed in claim 1 or 2 wherein said solvent is selected from acetone, 2-butanone, 3-pentanone, 2-pentanone or 2-hexanone.
4. A process as claimed in claim 3 wherein the amount of said solvent is 10 - 20 volumes for atorvastatin calcium form - I and 30 - 70 volumes for a mixture of crystalline and amorphous atorvastatin calcium.
5. A process as claimed in claim 4 wherein the amount of said solvent is 15 volumes of acetone for atorvastatin calcium form - I and 50 volumes of acetone for a mixture of crystalline and amorphous atorvastatin calcium.
6. A process as claimed in any preceding claim wherein acetone is removed under vacuum at 45 - 50 ^{0}C leaving behind 2 - 5 volumes of acetone.
7. A process as claimed in claim 6 wherein acetone is removed under vacuum at 45 - 50 ^{0}C leaving behind 2.5 - 3 volumes of acetone.
8. A process as claimed in claim 7 wherein acetone is further removed in vacuum dryer at 30 - 50 ^{0}C.
9. A process as claimed in claim 8 wherein acetone is further removed in vacuum dryer at 45 - 50 ^{0}C.
10. A process as claimed in any preceding claim wherein uniform powder is dried in vacuum dryer at 30 - 50 ^{0}C for 5 - 25 hours.
11. A process as claimed in claim 10 wherein uniform powder is dried in vacuum dryer at 45 - 50 ^{0}C for 10 - 15 hours.

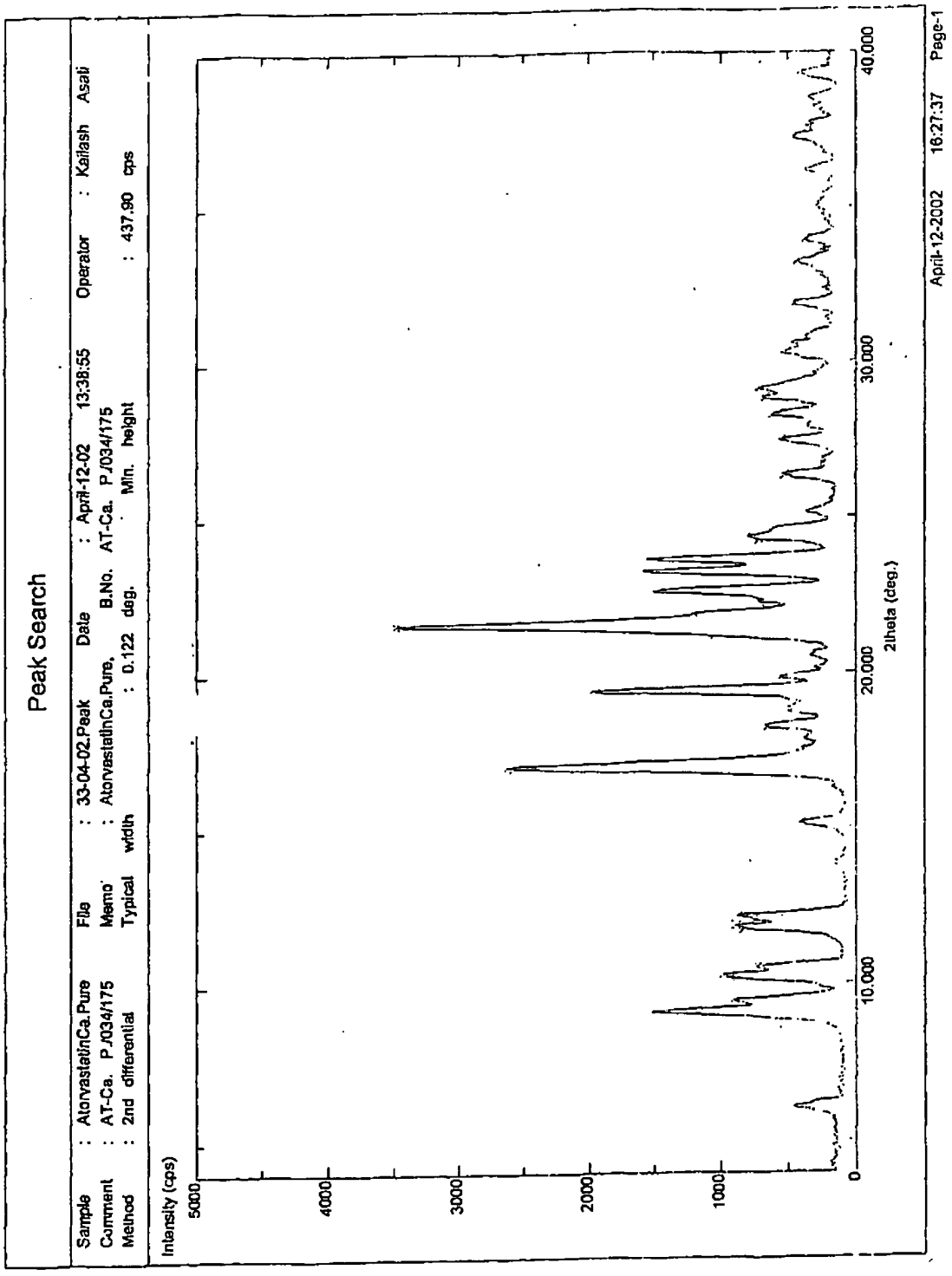
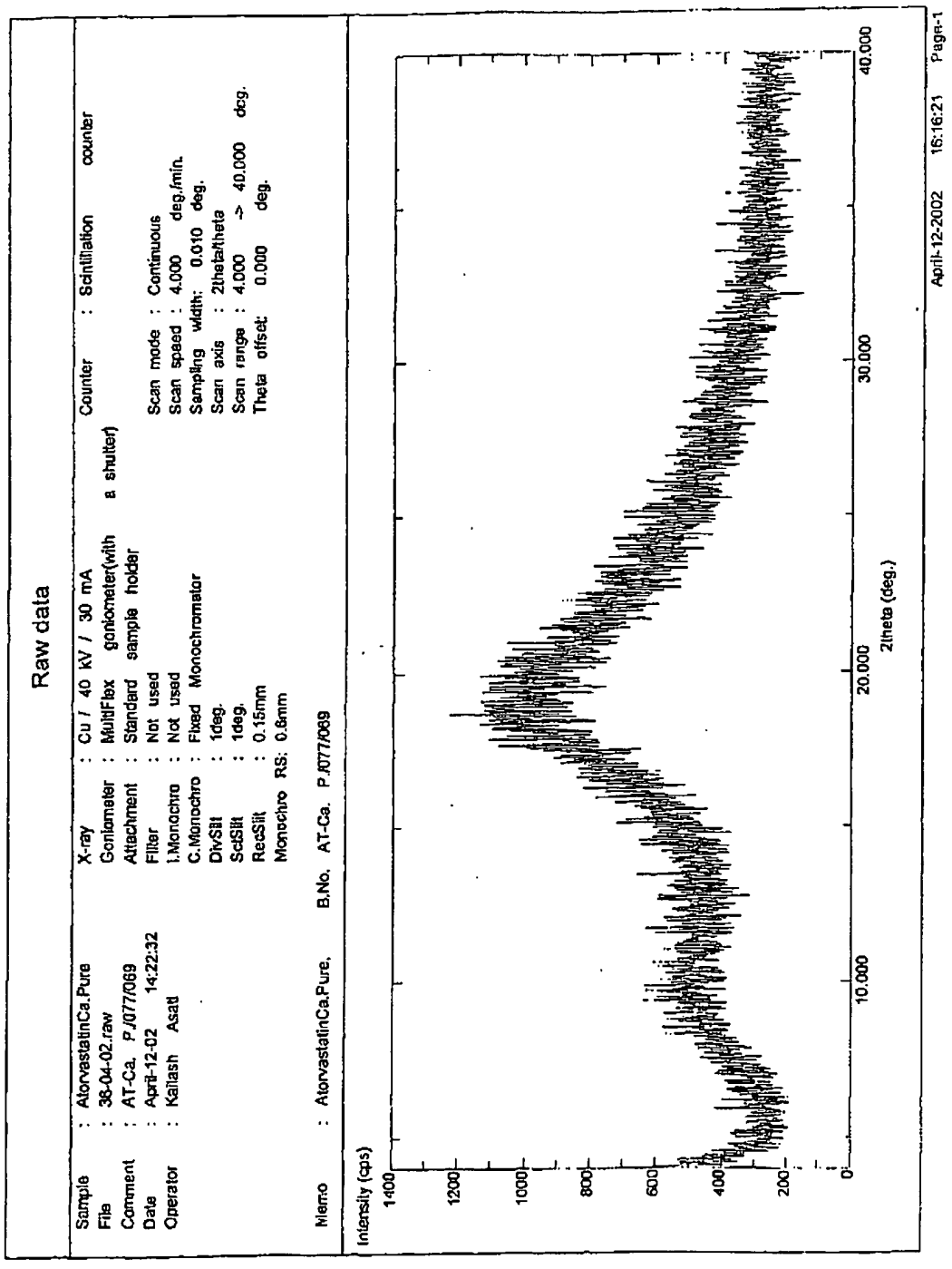

Peak Search
Sample : AtorvastatinCa.Pure
Comment : AT-Ca. PJ034/175
Method : 2nd differential
File : 33-04-02.Peak
Memo : AtorvastatinCa.Pure,
Typical width : 0.122 deg.
Date : April-12-02 13:38:55
B.No. AT-Ca. PJ034/175
Min. height : 437.90 cps
Operator : Kailash Asati
Intensity (cps)
5000
4000
3000
2000
1000
0
10.000
20.000
30.000
40.000
2theta (deg.)
April-12-2002 16:27:37 Page-1

Fig. 1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Comment : AT-Ca. P./077/069
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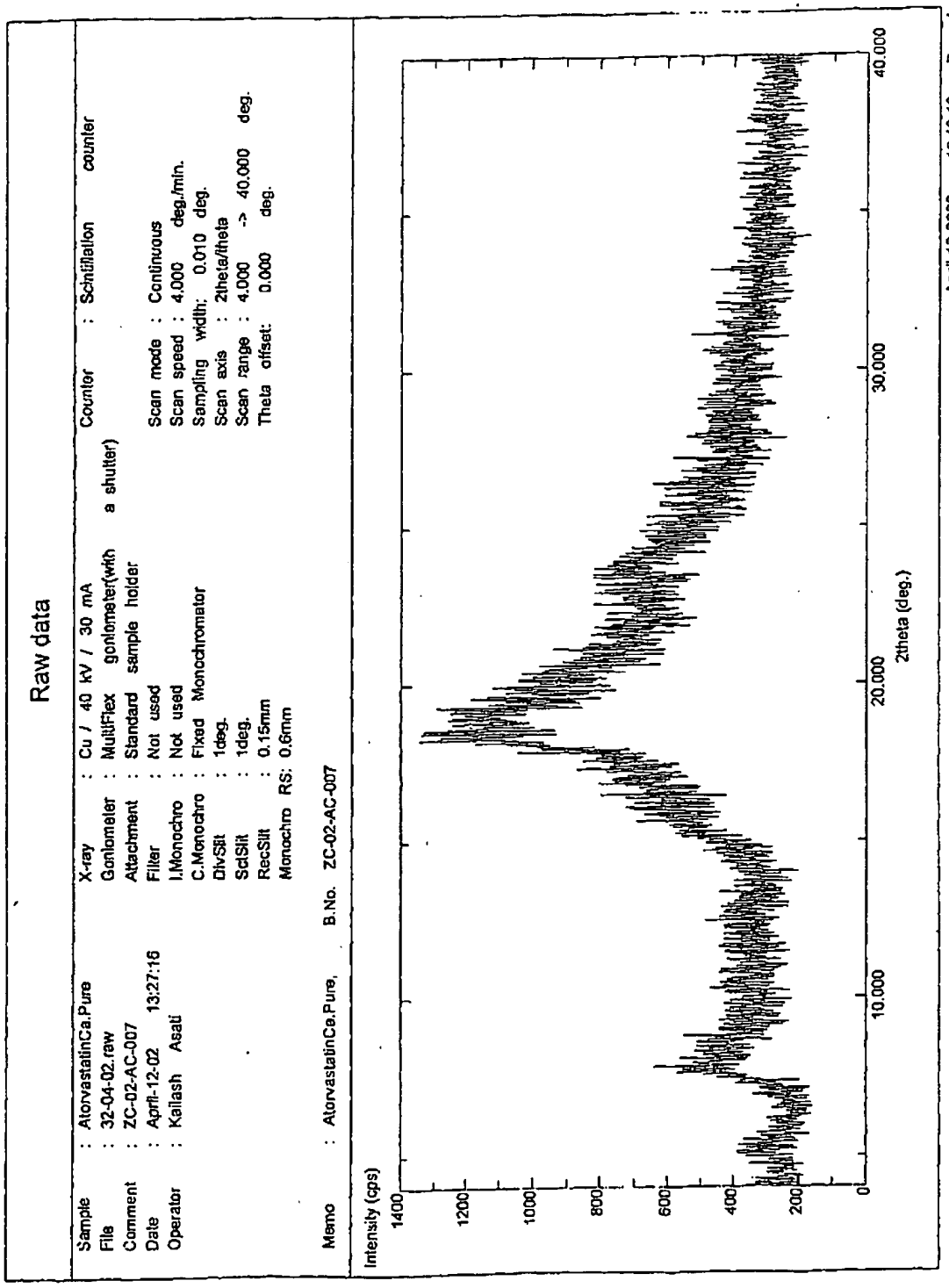
Operator : Kailash Asati
X-ray : Cu / 40 kV / 30 mA
Goniometer : MultiFlex goniometer(with a shutter)
Attachment : Standard sample holder
Filter : Not used
i.Monochro : Not used
C.Monochro : Fixed Monochromator
DivSlit : 1deg.
ScSlit : 1deg.
ReSlit : 0.15mm
Monochro RS: 0.6mm
Counter : Scintillation counter
Scan mode : Continuous
Scan speed : 4.000 deg./min.
Sampling width: 0.010 deg.
Scan axis : 2theta/theta
Scan range : 4.000 -> 40.000 deg.
Theta offset: 0.000 deg.
Memo : AtorvastatinCa.Pure, B.No. AT-Ca. P./077/069
Intensity (cps)
1400
1200
1000
800
600
400
200
0
10.000
20.000
30.000
40.000
2theta (deg.)
April-12-2002 16:16:21 Page-1

Fig. 2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Attachment : Standard sample holder
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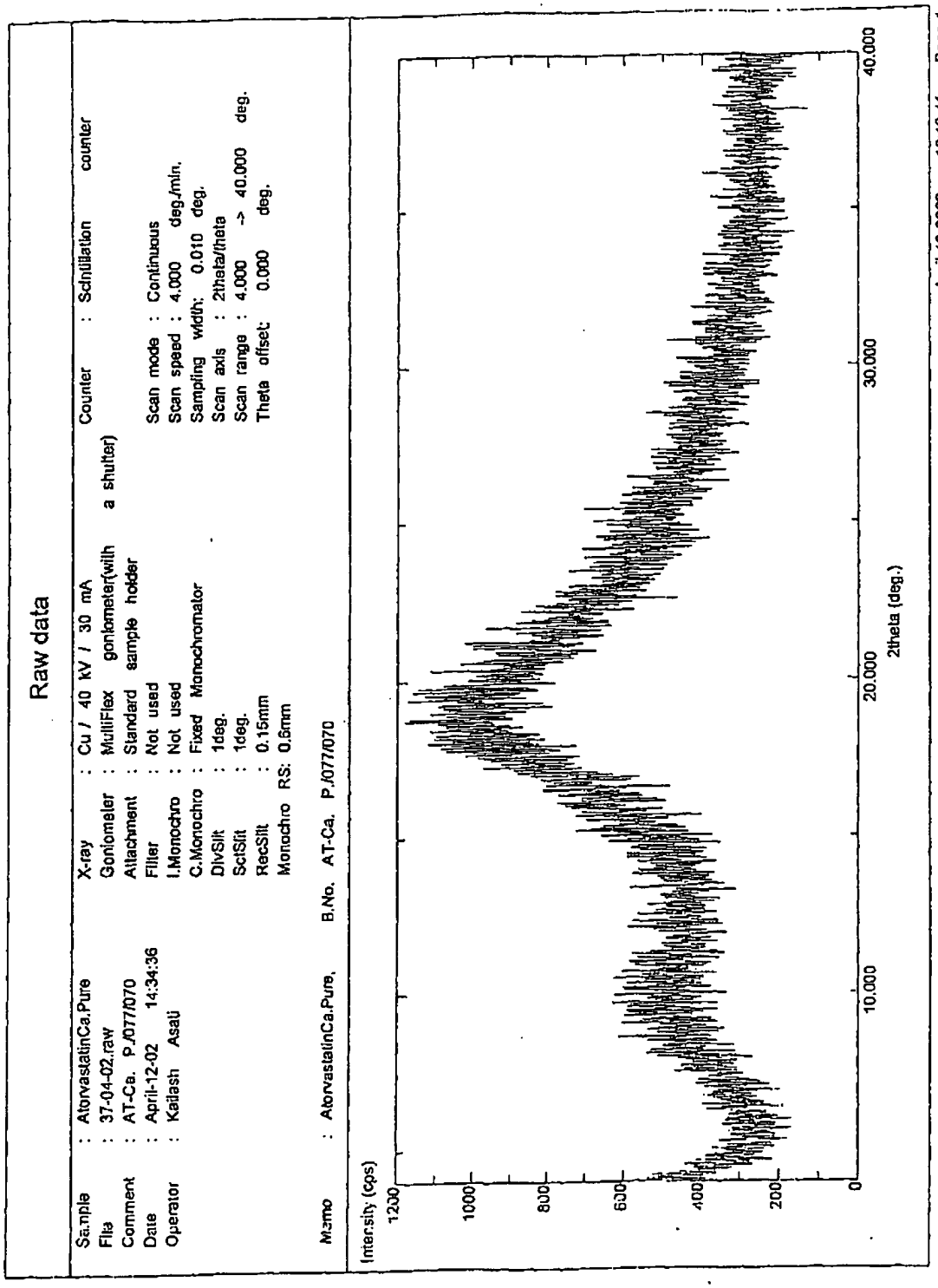
I.Monochro : Not used
C.Monochro : Fixed Monochromator
DivSlit : 1deg.
SctSlit : 1deg.
RecSlit : 0.15mm
Monochro RS: 0.6mm
Counter : Scintillation counter
Scan mode : Continuous
Scan speed : 4.000 deg./min.
Sampling width: 0.010 deg.
Scan axis : 2theta/theta
Scan range : 4.000 -> 40.000 deg.
Theta offset: 0.000 deg.
Memo : AtorvastatinCa.Pure, B.No. ZC-02-AC-007
Intensity (cps)
1400
1200
1000
800
600
400
200
0
10.000
20.000
30.000
40.000
2theta (deg.)
April-12-2002 16:13:13 Page-1

Fig. 3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Goniometer : MultiFlex goniometer(with a shutter)
Attachment : Standard sample holder
Filter : Not used
I.Monochro : Not used
C.Monochro : Fixed Monochromator
DivSlit : 1deg.
SctSlit : 1deg.
RecSlit : 0.15mm
Monochro RS: 0.6mm
Counter : Scintillation counter
Scan mode : Continuous
Scan speed : 4.000 deg./min.
Sampling width: 0.010 deg.
Scan axis : 2theta/theta
Scan range : 4.000 -> 40.000 deg.
Theta offset: 0.000 deg.
Memo : AtorvastatinCa.Pure, B.No. AT-Ca. P./077/070
Intensity (cps)
1200
1000
800
600
400
200
0
10.000
20.000
30.000
40.000
2theta (deg.)
April-12-2002 16:16:41 Page-1

Fig. 4

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/IN 02/00220

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2003	21/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/IN 02/00220

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

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Intern: Application No
PCT/IN 02/00220

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